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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/569,583	02/23/2006	Neil Gallagher	101213-1P US	5947

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EXAMINER	
HA, JULIE	
ART UNIT	PAPER NUMBER
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/569,583	GALLAGHER, NEIL	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *January 12, 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,9,11 and 24-28* is/are pending in the application.

4a) Of the above claim(s) *24-26 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 9, 11, 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment filed on January 12, 2007 is acknowledged. It is also acknowledged that claims 1-23 are not pending in the application as stated in the Restriction Requirement. Claims 10, 23 and 14 were cancelled in the Preliminary Amendment filed February 23, 2006. It is also acknowledged that Claims 1, 2-8, 10, 12-23 are cancelled and new claims 24-28 are added.

Restriction

1. Applicant's election without traverse of Group II (Claims 2 and 9) drawn to a combination comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide and a bisphosphonate in the reply filed on January 12, 2007 is acknowledged. As a single species, Applicants' election of pamidronic acid is acknowledged. Claims 24-26 and 28 are withdrawn from consideration drawn to non-elected species. Claims 2, 9, 11 and 27 are examined on the merits in this application.

Objection-Specification

2. The specification is objected to for not having the following arrangement. The Applicant is requested to correct the error as follows:

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Rejection-35 U.S.C. 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 2, 9, 11 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Janus et al (PG Pub 2002/0055457) in view of Curwen et al (Poster EORTC-NCI-AACR, 2002), Nelson et al (BJU International, 2000, 85(suppl 2), 45-48) and Walczak et al (Expert Opin. Investig. Drugs, 2002).

6. The instant claims are drawn to a combination comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl)phenyl)pyridine-3-sulfonamide and a bisphosphonate (pamidronic acid or a pharmaceutically acceptable salt thereof). The claims are additionally drawn to a pharmaceutical composition comprising a combination in association with a pharmaceutically acceptable diluent or carrier.

7. Janus et al (PG Pub 2002/0055457) discloses a method of inhibition of bond metastases including in cancer patients an effective amount of an endothelin ET-A receptor antagonist (see claim 1). The reference further teaches that the primary cancer is prostate cancer (see claim 4). Furthermore, the reference teaches that the method comprises administration of a therapeutic agent, bisphosphonate (see claim 9). The reference teaches that therapeutic

agent (bisphosphonate) addition impedes net bone loss (see claim 8). Additionally, the reference teaches the pharmaceutical formulations, the compounds may be administered orally, buccally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles (see paragraphs [0115] and [0117]). This reads on claims 2 and 11. The difference between the reference and the instant claims is that the reference does not teach N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide.

8. However, Curwen et al (Poster, 2002) teach that ZD4054 (N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide), a specific endothelin A receptor antagonist has utility in prostate cancer and metastatic bone disease (see poster, Figure 1, Results and Discussion). The reference further teaches that in *in vitro* studies, ZD4054 is a high-affinity ligand for the human ET_A receptor, with a pIC_{50} value of 8.27, while ZD4054 had no measurable affinity for the ET_B receptor (see Results, In vitro radioligand binding studies). Additionally, the reference teaches that ZD4054 is a potent ETA receptor antagonist in vivo, producing a dose-related response (see Figure 2a and Results, Intravenous antagonist potency).

9. Nelson et al (BJU International, 2000) teach that the endothelin (ETs) are identical in all mammals and many higher vertebrates; the ET receptors are also very similar (see p. 45, left column, 2nd paragraph). Additionally, the reference teaches that every prostate cancer cell line tested produces ET-1 mRNA and

protein (see p.45, right column, 2nd paragraph). Furthermore, the reference teaches that using a selective ET_A receptor antagonist, the abdominal constrictor response of mice to ET-1 was completely inhibited (see pp. 46, right bottom paragraph and p. 47, top left paragraph).

10. Walczak et al (Expert Opin. Investig. Drugs, 2002) teach that men with hormone-independent prostate cancer are at risk for skeletal morbidity (see p. 1742, 1st 2 lines of 4. Bone-targeted therapy). The reference further teaches that bisphosphonates exert their action by inducing apoptosis of osteoclasts. Bisphosphonates have demonstrated in vitro inhibitory effect on breast and prostate cancer cell adhesion to bone, and a direct cellular effect in inhibiting tumor cell invasion and proteolytic activity of matrix metalloproteinases. Pamidronate disodium and zoledronic acid have also shown in vitro inhibition of prostate cancer cell growth (see p. 1742, section 4.1).

11. Therefore, it would have been obvious to the ordinary skilled in the art to combine the bisphosphonate and endothelin receptor antagonist. There is a reasonable expectation of success, since bisphosphonate is used in treatment of prostate cancer and endothelin receptor antagonist (ZD4054) is used in treatment of prostate cancer, thus combining the two into a combination compound would show at least an additive effect. Additionally, the ordinary skilled artisans would be motivated to combine the teachings of the prior arts because Curwen et al teach that ZD4054 is a high-affinity ligand for the human ET_A receptor, with a pIC_{50} value of 8.27, while ZD4054 had no measurable affinity for the ET_B receptor. Furthermore, Janus et al teach that bisphosphonate

addition impedes bone loss (see claim 8). Therefore, since ZD4054 is selective for ET_A receptor, one would expect it to be active.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Julie Ha
Patent Examiner
AU1654

3/5/09
ANISH GUPTA
PRIMARY EXAMINER